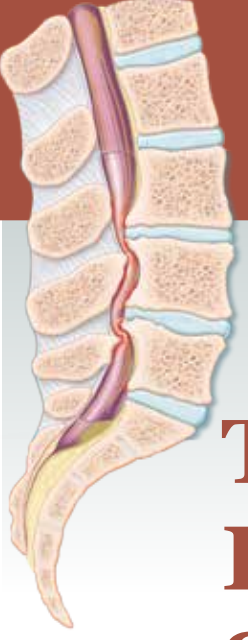

The Canadian Spine Surgeon's Perspective: Avoiding Opioid Use in Spine Patients

ABSTRACT

Opioids are drugs with pain relieving properties; however, there is evidence that opioids are no more effective than non-opioid medications in treating low back pain (LBP), and opioid use results in higher adverse events and worse surgical outcomes. First line treatment should emphasize non-pharmacological modalities including education, self-care strategies, and physical rehabilitation. Non-steroidal anti-inflammatory drugs (NSAIDs) are generally considered an appropriate introduction into pharmacological treatment when deemed necessary. Non-opioid adjunct medications can be considered for specific features related to LBP such as neuropathic leg pain. Primary care providers should exhaust first and second line treatments before considering low-dose opioids, and only then in consultation with evidence-based clinical practice guidelines.

KEYWORDS: Pharmacological; low back pain; radiculopathy; opioids; analgesia

CME Pre-test Quiz

Introduction

Opioid misuse in patients presenting to spine surgery clinics in Canada is a major problem. An analysis of elective thoracolumbar spine surgery patients in the Canadian Spine Society (CSS) national registry revealed that 35% of the patients were taking opioids on a daily basis prior to surgery. A further 20% indicated that

Alexandra Stratton, MD MSc FRCSC, *Orthopaedic Spinal Surgeon, University of Ottawa Combined Adult Spinal Surgery Program, Division of Orthopaedic Surgery, The Ottawa Hospital, Ottawa, ON.*
Dr. Darren Roffey, *University of Ottawa Spine Program, The Ottawa Hospital, Ottawa, ON, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON.*
Dr. Erica Stone, MD, FRCPC, *Anesthesiology, PGY 6 Pain Medicine, The Ottawa Hospital, Ottawa, ON.*
Mohamed M. El Koussy, BSc, *Clinical Research Assistant, University of Ottawa Combined Adult Spinal Surgery Program, Division of Orthopaedic Surgery, The Ottawa Hospital, Ottawa, ON.*
Dr. Eugene Wai *is an orthopedic surgeon who specializes in the care of adult spinal disorders. He is also an Associate Professor in the Department of Surgery at the University of Ottawa. In addition he is the Research Chair for the Canadian Spine Society.*

they took opioids intermittently. There are many plausible explanations for these findings, one of which is the length of time patients in Canada wait to see a spine surgeon. This wait time can lead to condition deterioration, multiple emergency room visits and pressure on the primary care provider to alleviate pain. Unfortunately, despite increased awareness in the medical community and attempts to curb opioid use, the proportion of patients taking opioids upon presentation for consultation with CSS member spine surgeons has remained unchanged in recent years. Importantly, 30% of all spine surgery patients in the registry continue taking opioids at one-year post-surgery.

The high daily or intermittent opioid use is concerning for many reasons. Firstly, the longer the duration patients take opioids pre-operatively, the more likely the patients are to remain users post-operatively.[1] Secondly, peri-operative pain is difficult to control in patients on pre-operative opioids compared to opioid naïve patients,[2] which represents a possible reason why hospital length of stay (LOS) is increased in this population.[3] Thirdly, and arguably most importantly, post-operative clinical outcomes and return to work rates are worse in patients on pre-operative opioids compared to non-users.[4–6]

In May 2017, a new Canadian guideline for opioid therapy for non-cancer pain was released.[7] These guidelines provide recommendations for trial opioids and at what dose, when to avoid opioids and how to taper these medications. A similar systematic review from the American College of Physicians (ACP) Clinical Practice Guideline was also released in April 2017 to address pharmacological options for low back pain (LBP).[8] These two publications provide an in-depth investigation and scrutiny of individual studies and overall levels of evidence pertaining to a wide range of pharmacotherapies. The focus of this article is to review the literature pertaining to non-opioid analgesia from the perspective of Canadian spine surgeons. Studies and classes of drugs chosen for this review reflect the medications patients who present to specialist spine surgery clinics commonly take and their benefits (or lack thereof).

Specifically, we aim to provide a step-wise approach for primary care providers to manage these patients while they wait for spine surgery consultation and to help in the long-term management of those patients for whom surgery is not an option. Furthermore, with the dosing recommendations outlined, we aim to assist providers prescribe these medications in a gradual, well-tolerated fashion. Drug doses were taken from the Compendium of Pharmaceuticals and Specialties (CPS)[9] and modified with input from an anesthesiologist specializing in chronic (non-cancer) pain management.

First line therapy: Non-pharmacological treatment

Multidisciplinary non-pharmacological treatment modalities and lifestyle modifications play an extremely important role in symptom management of LBP and related pathologies (e.g. stenosis, radiculopathy).

Non-pharmacological modalities consist of education, activity normalization and pacing, prescribed exercise, self-care strategies and physical rehabilitation, as outlined in the Toward Optimized Practice (TOP) guideline,[10] and should be initiated as first line therapy prior to embarking upon any pharmacological treatment.

Second line therapy: Non-steroidal anti-inflammatories (NSAIDs)

Key evidence-based findings:

Clinical studies:

- Diclofenac and ibuprofen were compared to placebo in an RCT designed to assess efficacy and safety in 372 patients with moderate to severe acute LBP.[11] Diclofenac was administered as two tablets initially (12.5mg each), followed by one or two every four to six hours as needed, up to a maximum of six tablets (75mg) per day for seven days. Ibuprofen 200mg tablets were administered in a similar fashion (maximum 1200mg/day). Diclofenac was deemed an effective and safe treatment for acute LBP; both medications demonstrated superiority over placebo in global efficacy.
- Naproxen alone was compared to naproxen with cyclobenzaprine and naproxen with oxycodone/acetaminophen in an RCT of 323 patients with acute non-traumatic LBP. All patients received naproxen 500mg twice daily, and were randomized to additionally receive one to two tablets of either placebo, cyclobenzaprine (5mg) or oxycodone/acetaminophen (5mg/325mg) every eight hours as needed.[12] All patients demonstrated clinically important improvement at seven days as noted on a disability questionnaire; however, there was no between-group difference, indicating naproxen alone was as effective as with the addition of muscle relaxant or opioid.
- In an RCT of 50 patients with chronic non-specific LBP randomized to receive either celecoxib (200mg twice daily) or acetaminophen (500mg twice daily) for four weeks, celecoxib was more effective than acetaminophen for back pain, including nocturnal pain and showed improved disability scores.[13]

Systematic reviews:

- A systematic review of the use of topical NSAIDs in painful musculoskeletal disorders including low back pain found topical NSAIDs to be ineffective in acute and chronic low back pain.[14]

Dosing recommendations:

- Diclofenac: 50-100mg daily or 50mg twice daily (maximum 100mg/day)
- Diclofenac slow-release: 75-100mg daily
- Naproxen: 375-500mg twice daily
- Celecoxib:
  - Acute pain: day 1—400mg single dose, day 2 onward—200mg once or twice daily as needed (maximum 400mg/day up to 7 days),
  - After 7 days: 100mg twice daily (maximum 200mg/day)

When to avoid:

- advanced renal or hepatic disease
- history of gastrointestinal disease (e.g. bleeding or ulcers)
- concurrent aspirin therapy or anti-coagulants
- elderly patients

Contraindications:

- hypersensitivity to the medication, aspirin, or other NSAIDS
- perioperative setting of coronary artery bypass graft surgery
- third trimester of pregnancy, women who are breastfeeding
- uncontrolled heart failure
- active GI bleed, active gastric/duodenal/peptic ulcer
- history of gastric bypass surgery
- recent large bowel surgery (with anastomosis)

Common side effects:

- Diclofenac and Naproxen: pruritus, rash, dizziness, headache, nausea/vomiting, dyspepsia, abdominal pain, vertigo
- Celecoxib: peripheral edema, dizziness, fever, headache, insomnia, rash, abdominal pain, nausea, vomiting, aggravation of hypertension (<2%)

Adjunct second line therapy: Antidepressants

Key evidence-based findings:

Clinical studies:

- In a randomized control trial (RCT), Kalita et al. compared amitriptyline at an initial dose of 12.5mg/day, doubled every two weeks to a maximum of 50mg/day, to pregabalin at an initial dose of 150mg/day, doubled every two weeks to a maximum of 600mg/day; amitriptyline had a positive effect on pain at baseline compared to follow up and was more effective than pregabalin.[17]
- Schreiber et al. conducted an RCT in forty non-depressed patients with LBP and whiplash associated cervical pain comparing amitriptyline, at an initial dose of 25mg/day increasing every other day to a maximum of 50-75mg/day, to fluoxetine at 20mg/day[16] and found no significant between-group differences, however 82% (amitriptyline group) and 77% (fluoxetine group) of patients had moderate to good pain relief.
- Stein et al. compared amitriptyline, at an initial dose of 37.5mg/day increasing to 150mg/day in four days, to 2000mg/day of paracetamol in an RCT and showed that amitriptyline was more effective at reducing pain intensity.[18]
- The above three trials suggest that amitriptyline, a tricyclic antidepressant (TCA), is a reasonable option for managing LBP. If the side effects are intolerable, a non-TCA antidepressant such as duloxetine may be equally effective in the management of chronic LBP.[8,19]

Dosing recommendations:

- Amitriptyline: 10mg at bedtime, increasing weekly by 10-25mg per dose, up to a maximum of 150mg/day
- Duloxetine: starting at 30mg daily, increasing to 60mg once daily as tolerated

When to avoid:

- patients with co-existing depression or anxiety and have been prescribed other psycho-tropic medications
- patients taking other serotonergic agents to avoid precipitating serotonin syndrome
- patients with ventricular dysrhythmias and QT prolongation

Contraindications:

- hypersensitivity to the medication
- either currently receiving or recently discontinued monoamine oxidase inhibitors (MAOIs)
- recovery phase following myocardial infarction (MI)

Common side effects:

- Amitriptyline: anticholinergic side effects (e.g. dry mouth, somnolence/drowsiness, constipation), memory impairment
- Duloxetine: headache, dizziness, insomnia, memory impairment, sexual dysfunction

Adjunct second line therapy: Muscle relaxants

Key evidence-based findings:

Clinical studies:

- Cyclobenzaprine is the muscle relaxant that has been most extensively studied in LBP patients. Two large RCTs with a total of 1,405 patients have investigated short-term (one week, three times a day) use of cyclobenzaprine in the absence of other analgesics for acute low back and neck pain.[20] The doses studied were: 2.5, 5 and 10mg versus placebo. At the 2.5mg TID dose (which is not available in Canada), cyclobenzaprine was no more effective than placebo; however, at 5mg and 10mg TID doses, cyclobenzaprine demonstrated benefit over placebo in managing neck and low back pain. Furthermore, the 5mg TID dose was as effective as 10mg TID, and was better tolerated.
- A more recent RCT studied the use of cyclobenzaprine, 5-10mg every eight hours on an as-needed basis added to naproxen 500mg twice daily, and found that cyclobenzaprine was no more effective than naproxen alone.[12] This discrepancy could be related to the difference in the dosing regimen compared to the previous studies (i.e. three times daily for seven days versus as-needed, taken alone versus in conjunction with naproxen).

Systematic reviews:

- There is little evidence to support the use of muscle relaxants in patients with non-acute LBP,[21] or the

use of muscle relaxants for longer than two to three weeks.

Dosing recommendations:

- Cyclobenzaprine: 5mg TID, for short term use (no more than three weeks)

When to avoid:

- elderly patients
- patients with hepatic impairment
- patients with non-acute LBP

Contraindications:

- hypersensitivity to the medication
- concomitant use of MAOIs
- hyperthyroidism
- congestive heart failure, arrhythmias, heart block or conduction disturbances, acute recovery phase of MI

Common side effects:

- Cyclobenzaprine: somnolence/drowsiness, dry mouth, dizziness, confusion, anxiety

Adjunct second line therapy: Gabapentinoids

Key evidence-based findings:

Clinical studies:

- In a study of 331 patients with putative radicular lower limb (below the knee) pain in addition to chronic LBP, whereby the leg pain was of at least a moderate level and was refractory to analgesics, the addition of pregabalin to the patients' analgesic regimen was more effective than "usual care".[23] Pregabalin dosing ranged from 25mg/day to 300mg/day. At baseline, patients in the pregabalin group had higher pain scores but pain, sleep and function were all improved at the four and eight week time points. While the dose was not standardized, this range reflects what is commonly seen by Canadian spine surgeons.
- A prospective study of 77 patients presenting to a specialist spine clinic looked at the addition of gabapentin to patients' pre-existing analgesic regimen including amitriptyline (10-50mg/day). Gabapentin was added at a dose of 300mg once daily for four days, 300mg twice daily for four days and 300mg three times daily thereafter, up to a maximum of 1800mg/day.[24] While the majority of patients reported a decrease in pain and disability scores at three months compared to the prior treatment without gabapentin, there was reduced effectiveness in the 53% of patients who experienced one or more side effects. The most common side effect was dizziness, reported in 27% of patients on combination treatment.

Systematic reviews:

- A recent systematic review and

meta-analysis of RCTs studying gabapentinoids in chronic LBP found minimal effect on pain, and a high incidence of adverse effects.[22] Consequently, the authors cautioned against the use of these medications in patients with predominant chronic back dominant pain.

Clinical pearl:

- The DN4 is a simple diagnostic tool developed for differentiating neuropathic from non-neuropathic pain.[25] A score of 4 or higher out of 10 is consistent with neuropathic pain and may be used as a threshold for when to prescribe gabapentinoids.

Dosing recommendations:

- Pregabalin: 25mg at night, increased weekly as tolerated by 25-75mg per day until on 225mg twice daily or 150mg three times daily (450mg/day)
- Gabapentin: 300mg at night, increased every five days as tolerated by 300mg per day to a maximum of 1200mg three times daily (3600mg/day)

When to avoid:

- chronic LBP with a score of 3 or less on the DN4

Contraindications:

- hypersensitivity to the medication
- renal impairment

Common side effects:

- both gabapentin and pregabalin: dizziness, somnolence, confusion/memory disturbance, impaired thinking, ataxia, nausea, fatigue, headache, nystagmus, peripheral edema
- pregabalin: weight gain

Other: Cannabinoids

Key evidence-based findings:

Clinical studies:

- A recent RCT included 30 patients with chronic back pain refractory to conventional treatment with NSAIDs and/or opioids.[27] Nabilone, a synthetic cannabinoid, at 0.25-1mg/day was compared to placebo. Nabilone treatment was superior in the reduction of spinal pain intensity, and four times more patients favoured nabilone over placebo.
- An increasing number of patients are presenting to spine surgery clinics having tried cannabinoids or with questions about this class of medication. To date, the evidence is scarce in patients with spinal pathology, however the TOP guidelines suggest that cannabinoids may be considered in the setting of neuropathic pain after three or more medications have been tried without success.[28]

Dosing recommendations:

- Nabilone: 0.5-1mg at night, increase to twice or three times daily as tolerated

Caution in:

- patients with psychiatric disorders or a history of psychosis
- elderly patients

Contraindications:

- hypersensitivity to any cannabinoid
- severe cardiovascular, immunological, liver, or kidney disease, especially in acute illness
- history of arrhythmias

Common side effects:

- dizziness
- dry mouth
- fatigue

Discussion

The results of a 12-month pragmatic randomized trial were recently published in March 2018.[29] This study design allowed flexibility in medication selection and dosage. Nonpharmacological pain therapies, an essential initial management strategy for back pain was not considered. The study compared opioid to non-opioid medications on pain-related function in 240 patients with moderate to severe chronic back pain or hip or knee osteoarthritis. Patients in the opioid group first received immediate-release opioids, followed by sustained action opioids when required, and as a third step—transdermal fentanyl. In the non-opioid group, patients received acetaminophen and NSAIDs as a first step, nortriptyline, amitriptyline or gabapentin and topical analgesics as a second step, and as a third step—pregabalin, duloxetine or tramadol. The trial showed that opioid therapy did not result in superior pain-related function compared to treatment with non-opioid analgesics. Furthermore, the opioid group experienced significantly more adverse medication-related symptoms.

As the risks associated with opioid use become clearer, optimizing non-opioid analgesia in patients with spine pathology should be a joint goal of primary care providers and spine surgeons, regardless of whether or not patients require surgical intervention.

As clinicians, it is vital that we share the responsibility of maximizing non-operative management of spinal pathologies. This strategy includes exhausting non-pharmacological treatment modalities as outlined in the TOP guideline,[10] and exploring appropriate pharmacological therapies as required.

In Figure 1, we have outlined a stepwise approach to managing patients with low back and radicular leg pain when non-pharmacological with or without acetaminophen (first-line) treatments fail to provide adequate pain relief. Second line treatment includes NSAIDs with consideration given to proton pump inhibitor to minimize gastro-intestinal side effects. Prior to initiating opioids, the following adjuncts to NSAIDs may be helpful: skeletal muscle relaxants (short term use only, maximum 3 weeks), gabapentinoids for leg dominant radicular pain (beginning with a very low dose and gradually increasing as tolerated), and antidepressants. Only after exhausting first and second line medications should low-dose opioids be considered. Clinicians are strongly encouraged to consult the Canadian guidelines[7] before initiation.

Figure 1: A Step-Wise Approach to Managing Low Back and Radicular Pain

Recommendations Consistent with CPG for Low Back and Radicular Leg Pain		
First Line	Second Line	Third Line
Optimize Non-Pharmacological Treatments [10] Consider Acetaminophen*	NSAIDs [10,30,31] (Ibuprofen, Diclofenac) or Cox 2 Inhibitors	Carefully consider low dose opioids for leg dominant pain (Tramadol, Tapentadol) using Canadian National Opioid Guidelines [7]

Adjunct Second Line Recommendations for Specific Spinal Conditions			
Prominent Muscle Spasms [10,32]	Neuropathic or Sciatic Leg Pain [33]	Chronic Low Back Pain	Chronic Pain with Sleep Disturbance and/or Fibromyalgia [34]
Skeletal Muscle Relaxants (Cyclobenzaprine)	Gabapentinoids** (Pregabalin, Gabapentin) or Antidepressants** (Duloxetine, Amitriptyline)	Antidepressants** (Duloxetine,[35] Amitriptyline[10])	Antidepressants** (Duloxetine, Amitriptyline) or Gabapentinoids** (Pregabalin, Gabapentin)

CPG=Clinical Practice Guidelines; LBP=Low Back Pain

*Some CPGs [2,3] recommend against Acetaminophen because placebo controlled trials have failed to show a benefit but note that there are no higher adverse events rates associated with acetaminophen use.[30,35]

**The American College of Physicians (ACP) guidelines note that there is insufficient evidence on the efficacy of antidepressants (except Duloxetine), or gabapentinoids.[35] The NICE LBP guidelines recommend against antidepressants or gabapentinoids for LBP, but do recommend these medications for neuropathic pain including sciatica.[30]

References

1. Connolly J, Javed Z, Raji MA, Chan W, Kuo Y-F, Baillargeon J. Predictors of Long-term Opioid Use Following Lumbar Fusion Surgery. Spine (Phila Pa 1976). 2017;42(18):1405-1411. doi:10.1097/BRS.0000000000002133.
2. Hina N, Fletcher D, Poindessous-Jazat F, Martinez V. Hyperalgesia induced by low-dose opioid treatment before orthopaedic surgery. Eur J Anaesthesiol. 2015;32(4):255-261. doi:10.1097/EJA.0000000000000197.
3. Armaghani SJ, Lee DS, Bible JE, et al. Preoperative Opioid Use and Its Association With Perioperative Opioid Demand and Postoperative Opioid Independence in Patients Undergoing Spine Surgery. Spine (Phila Pa 1976). 2014;39(25):E1524-E1530. doi:10.1097/BRS.0000000000000622.
4. Todd J, Lawrence R, London N, Bohlman HH, Chin KR. Preoperative Narcotic Use as a Predictor of Clinical Outcome Results Following Anterior Cervical Arthrodesis. Spine (Phila Pa 1976). 2008;33(19):2074-2078. https://insights-ovid-com.proxy.bib.uottawa.ca/pubmed?pmid=18758363.

DN4 – QUESTIONNAIRE

To estimate the probability of neuropathic pain, please answer yes or no for each item of the following four questions.

INTERVIEW OF THE PATIENT

QUESTION 1:

Does the pain have one or more of the following characteristics?	**YES**	**NO**
Burning	❑	❑
Painful cold	❑	❑
Electric shocks	❑	❑

QUESTION 2:

Is the pain associated with one or more of the following symptoms in the same area?	**YES**	**NO**
Tingling	❑	❑
Pins and needles	❑	❑
Numbness	❑	❑
Itching	❑	❑

EXAMINATION OF THE PATIENT

QUESTION 3:

Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?	**YES**	**NO**
Hypoesthesia to touch	❑	❑
Hypoesthesia to pinprick	❑	❑

QUESTION 4:

In the painful area, can the pain be caused or increased by:	**YES**	**NO**
Brushing?	❑	❑

YES = 1 point
NO = 0 points

Patient's Score: /10

SUMMARY OF KEY POINTS

1. First line treatment for low back and radicular leg pain is non-pharmacological.
2. Second line treatment includes NSAIDs (with or without proton pump inhibitor), and muscle relaxants (3 weeks maximum), gabapentinoids and antidepressants.
3. Exhausting non-opioid analgesics includes trialing different medications within the same class and at different doses since many of these medications have wide therapeutic dose ranges.

CME

Post-test Quiz

Members of the College of Family Physicians of Canada may claim MAINPRO-M2 Credits for this unaccredited educational program.

Accessed December 4, 2017.

5. Lee D, Armaghani S, Archer KR, et al. Preoperative Opioid Use as a Predictor of Adverse Postoperative Self-Reported Outcomes in Patients Undergoing Spine Surgery. J Bone Jt Surgery-American Vol. 2014;96(11):e89-1-8. doi:10.2106/JBJS.M.00865.
6. Villavicencio AT, Lee Nelson E, Kantha V, Burneikiene S. Prediction based on preoperative opioid use of clinical outcomes after transforaminal lumbar interbody fusions. J neurosurg Spine. 2017;26:144-149. doi:10.3171/2016.7.SPINE16284.
7. Busse JW, Craigie S, Juurlink DN, et al. Guideline for opioid therapy and chronic noncancer pain. CMAJ. 2017;189(18):E659-E666. doi:10.1503/cmaj.170363.
8. Chou R, Deyo R, Friedly J, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Ann Intern Med. 2017;166(7):480. doi:10.7326/M16-2458.
9. Compendium of Pharmaceuticals and Specialties (CPS) - English. https://www.pharmacists.ca/products-services/compendium-of-pharmaceuticals-and-specialties/. Accessed March 22, 2018.
10. EVIDENCE-INFORMED PRIMARY CARE MANAGEMENT OF LOW BACK PAIN Clinical Practice Guideline | December 2015. http://www.topalbertadoctors.org/download/1885/LBPguideline.pdf?_20180309014411. Accessed March 8, 2018.
11. Dreiser RL, Marty M, Ionescu E, Gold M, Liu JH. Relief of acute low back pain with diclofenac-K 12.5 mg tablets: a flexible dose, ibuprofen 200 mg and placebo-controlled clinical trial. Int J Clin Pharmacol Ther. 2003;41(9):375-385. http://www.ncbi.nlm.nih.gov/pubmed/14518597. Accessed March 6, 2018.
12. Friedman BW, Dym AA, Davitt M, et al. Naproxen With Cyclobenzaprine, Oxycodone/Acetaminophen, or Placebo for Treating Acute Low Back Pain. JAMA. 2015;314(15):1572. doi:10.1001/jama.2015.13043.
13. Bedaiwi MK, Sari I, Wallis D, et al. Clinical Efficacy of Celecoxib Compared to Acetaminophen in Chronic Nonspecific Low Back Pain: Results of a Randomized Controlled Trial. Arthritis Care Res (Hoboken). 2016;68(6):845-852. doi:10.1002/acr.22753.
14. Haroutiunian S, Drennan DA, Lipman AG. Topical NSAID Therapy for Musculoskeletal Pain. Pain Med. 2010;11(4):535-549. doi:10.1111/j.1526-4637.2010.00809.x.
15. van den Driest JJ, Bierma-Zeinstra SMA, Bindels PJE, Schiphof D. Amitriptyline for musculoskeletal com-

CLINICAL PEARLS

A "start low and go slow" approach is recommended for initiating pharmacological treatments for low back and radicular leg pain, especially when using neuroleptics and antidepressants.

When treating low back pain with neuropathic leg pain, patients who fail a trial of pregabalin may tolerate gabapentin, or vice versa.

Antidepressants have a role in managing low back pain, particularly chronic, even in the absence of mood disorder.

plaints: a systematic review. Fam Pract. 2017;34(2):138-146. doi:10.1093/fampra/cmw134.
16. Schreiber S, Vinokur S, Shavelzon V, Pick CG, Zahavi E, Shir Y. A randomized trial of fluoxetine versus amitriptyline in musculo-skeletal pain. Isr J Psychiatry Relat Sci. 2001;38(2):88-94. http://www.ncbi.nlm.nih.gov/pubmed/11475920. Accessed March 6, 2018.
17. Kalita J, Kohat AK, Misra UK, Bhoi SK. An open labeled randomized controlled trial of pregabalin versus amitriptyline in chronic low backache. J Neurol Sci. 2014;342(1-2):127-132. doi:10.1016/j.jns.2014.05.002.
18. Stein D, Peri T, Edelstein E, Elizur A, Floman Y. The Efficacy of Amitriptyline and Acetaminophen in the Management of Acute Low Back Pain. Psychosomatics. 1996;37(1):63-70. doi:10.1016/S0033-3182(96)71600-6.
19. Pergolizzi J V, Raffa RB, Taylor R, Rodriguez G, Nalamachu S, Langley P. A review of duloxetine 60 mg once-daily dosing for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain due to chronic osteoarthritis pain and low back pain. Pain Pract. 2013;13(3):239-252. doi:10.1111/j.1533-2500.2012.00578.x.
20. Borenstein DG, Korn S. Efficacy of a low-dose regimen of cyclobenzaprine hydrochloride in acute skeletal muscle spasm: results of two placebo-controlled trials. Clin Ther. 2003;25(4):1056-1073. http://www.ncbi.nlm.nih.gov/pubmed/12809957. Accessed March 6, 2018.
21. van Tulder MW, Koes B, Malmivaara A. Outcome of non-invasive treatment modalities on back pain: an evidence-based review. Eur Spine J. 2006;15(S1):S64-S81. doi:10.1007/s00586-005-1048-6.
22. Shanthanna H, Gilron I, Rajarathinam M, et al. Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-anaShanthanna, H., Gilron, I., Rajarathinam, M., AlAmri, R., Kamath, S., Thabane, L., … Bhandari, M. (2017). Benefits and safety of gabapentinoids in chronic low . Tsai AC, ed. PLoS Med. 2017;14(8):e1002369. doi:10.1371/journal.pmed.1002369.
23. Taguchi T, Igarashi A, Watt S, et al. Effectiveness of pregabalin for the treatment of chronic low back pain with accompanying lower limb pain (neuropathic component): a non-interventional study in Japan. J Pain Res. 2015;8:487-497. doi:10.2147/JPR.S88642.
24. Robertson KL, Marshman LAG. Gabapentin Superadded to a Pre-Existent Regime Containing Amytriptyline for Chronic Sciatica. Pain Med. 2016;17(11):2095-2099. doi:10.1093/pm/pnw052.
25. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114(1):29-36. doi:10.1016/j.pain.2004.12.010.
26. Fitzcharles M-A, Baerwald C, Ablin J, Häuser W. Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis): A systematic review of randomized controlled trials. Schmerz. 2016;30(1):47-61. doi:10.1007/s00482-015-0084-3.
27. Pinsger M, Schimetta W, Volc D, Hiermann E, Riederer F, Pölz W. Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain--a randomized controlled trial. Wien Klin Wochenschr. 2006;118(11-12):327-335. doi:10.1007/s00508-006-0611-4.
28. Toward Optimized Practice (TOP) - Medical Cannabinoids. http://topalbertadoctors.org/cpgs/?sid=18&cpg_cats=107&cpg_info=75. Accessed March 22, 2018.
29. Krebs EE, Gravely A, Nugent S, et al. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain. JAMA. 2018;319(9):872. doi:10.1001/jama.2018.0899.
30. Low back pain and sciatica overview - NICE Pathways. https://pathways.nice.org.uk/pathways/low-back-pain-and-sciatica. Accessed March 8, 2018.
31. Neuropathic pain – pharmacological management The pharmacological management of neuropathic pain in adults in non-specialist settings NICE clinical guideline 173. 2013. http://guidance.nice.org.uk/CG173. Accessed March 8, 2018.
32. Low back pain and sciatica overview - NICE Pathways.
33. Neuropathic pain – pharmacological management The pharmacological management of neuropathic pain in adults in non-specialist settings NICE clinical guideline 173. 2013.
34. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017;76(2):318-328. doi:10.1136/annrheumdis-2016-209724.
35. Qaseem A, Wilt TJ, McLean RM, Forciea MA, Clinical Guidelines Committee of the American College of Physicians. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2017;166(7):514-530. doi:10.7326/M16-2367.